Neural predictors of cognitive-behavior therapy outcome in anxiety-related disorders: a meta-analysis of task-based fMRI studies

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Abstract

Background. Cognitive-behavior therapy (CBT) is a well-established first-line intervention for anxiety-related disorders, including specific phobia, social anxiety disorder, panic disorder/agoraphobia, generalized anxiety disorder, obsessive-compulsive disorder, and posttraumatic stress disorder. Several neural predictors of CBT outcome for anxiety-related disorders have been proposed, but previous results are inconsistent. **Methods**. We conducted a systematic review and meta-analysis of task-based functional magnetic resonance imaging (fMRI) studies investigating whole-brain predictors of CBT outcome in anxiety-related disorders (17 studies, n=442). **Results.** Across different tasks, we observed that brain response in a network of regions involved in salience and interoception processing, encompassing fronto-insular (the right inferior frontal gyrus-anterior insular cortex) and fronto-limbic (the dorsomedial prefrontal cortex-dorsal anterior cingulate cortex) cortices was strongly associated with a positive CBT outcome. **Conclusions**. Our results suggest that there are robust neural predictors of CBT outcome in anxiety-related disorders that may eventually lead (probably in combination with other data) to develop personalized approaches for the treatment of these mental disorders.

Keywords: anxiety disorders; meta-analysis; task-based fMRI; cognitive-behavioral therapy; treatment response prediction; salience network

Introduction

Anxiety-related disorders - including specific phobia (SP), social anxiety disorder (SAD), panic disorder/agoraphobia (PDA), generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD)- are common mental disorders that impose a severe toll on both individuals and society (Whiteford *et al.* 2013). Cognitive-behavior therapy (CBT) is a form of psychological treatment that is well established as a first-line intervention for all anxiety-related disorders (Hoffman & Smits 2008). However, nearly a half of patients with anxiety-related disorders who receive CBT do not show significant improvement (Loerinc *et al.* 2015). Therefore, an important focus of current research is the search for baseline variables indicating the likelihood that a patient will do better or worse with a particular treatment (i.e., treatment outcome predictors). Neuroimaging is one approach that has demonstrated promise in the search for such predictors.

Several individual studies have identified structural and functional neuroimaging predictors of CBT outcomes across these disorders. Regarding functional magnetic resonance imaging (fMRI) studies, baseline (pre-treatment) activity in brain regions involved in visual and emotional processing, emotion regulation, and inhibition have been linked to CBT outcome/response. The results of this work have been *qualitatively* summarized in several systematic reviews (Chakrabarty *et al.* 2016; Lueken *et al.* 2016; Colvonen *et al.* 2017). There have been, however, few attempts to provide a *quantitative* summary of this research, for example, via meta-analysis of imaging findings. A notable exception is the study by Marwood et al. (2018). This meta-analysis included 11 whole-brain task-based fMRI studies (n=293 patients) with anxiety-related or depressive disorders. The authors found that activation of the right cuneus

(i.e., the visual cortex) was the only robust predictor of psychotherapy outcome, with greater activation at baseline predicting greater improvement. However, there were signs of publication bias in these results (Marwood *et al.* 2018). Moreover, this meta-analysis relied exclusively on peak coordinates reported in published papers, i.e., did not include statistical parametric maps (SPMs). Including SPMs substantially increases statistical power and may mitigate against reporting biases (Radua *et al.* 2012). Likewise, this meta-analysis included studies of diverse treatment approaches across anxiety-related and depressive disorders, potentially increasing heterogeneity. Although most psychological therapies share common elements (Wampold 2015), there are also theoretical and practical differences *between* different therapies (e.g., CBT versus psychodynamic psychotherapy) (e.g., Barlow, 2004).

CBT for anxiety-related disorders includes mainly exposure and cognitive restructuring techniques. Exposure involves repeatedly confronting feared/avoided situations and is based upon the principles of fear extinction learning (Pittig *et al.* 2016; Wenzel 2017). Cognitive restructuring consists of evaluating and modifying maladaptive thoughts and beliefs, and is considered to be a cognitive reappraisal approach (i.e., reframing an event in order to change one's emotional response to it) (Gross 2014). Extinction learning and cognitive reappraisal have been thoroughly investigated using fMRI. Although the two processes consistently engage some similar brain regions (the dorsal anterior cingulate cortex, dACC, and the bilateral anterior insular cortex, AIC), extinction is more consistently linked to activation of sensory and emotion processing regions, whereas re-appraisal is more consistently associated with activation of a dorsal fronto-parietal network (Picó-Pérez *et al.* 2019).

Here, we present the results of a pre-registered systematic review and meta-analysis of neural predictors of CBT outcome in anxiety-related disorders as assessed across task-based

fMRI studies. We focused on three processes that are conceptually related to the mechanisms of action of CBT, and the most frequently used to predict response to CBT in the literature (emotion processing, emotion regulation, and inhibition/interference). Our goal was to identify patterns of pre-treatment brain activation and/or deactivation that most consistently predict CBT outcome across anxiety-related disorders, as well as to assess the robustness of these results.

Methods

The meta-analysis was conducted according to PRISMA guidelines (http://www.prismastatement.org/). Details of the meta-analysis were registered at PROSPERO, an international prospective register of systematic reviews/meta-analysis (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=82239). We note that in the original preregistration of the meta-analysis the goal was to include both depressive and anxiety-related disorders, but after the publication of Marwood et al. (2018), we decided to focus on anxiety-related disorders. All procedures were performed in accordance with recent recommendations for neuroimaging meta-analyses (Müller *et al.* 2018).

Literature search and study selection

A comprehensive literature search using PubMed was conducted for English-language peer-reviewed studies investigating task-based fMRI baseline predictors of CBT outcome in adult (age > 18 years) patients with diagnosed anxiety-related disorders (including SP, SAD, PDA, GAD, OCD, and PTSD), and published between January 1998 and 30th April 2021. The search terms were: "fMRI" OR "magnetic resonance imaging", "psychotherapy" OR "psychological treatment" OR "(cognitive) behavior therapy", and "prediction". Returned articles were manually

inspected for additional studies. Researchers in the field were contacted about potential unpublished data. Corresponding authors were contacted regarding their willingness to share original brain statistical maps or to provide whole brain analysis results if these maps were not available.

All voxel-wise studies assessing the relationship between task-evoked brain activation/deactivation at baseline and the response to CBT at the whole-brain level were included, either if they compared activation/deactivation between CBT-responders and non-CBT-responders (with a pre-established "response" criterion) or if they correlated brain activation/deactivation with the degree of response to CBT (i.e., the severity change from pre to post CBT). Conversely, studies were excluded if they used other approaches (e.g., machine learning) or did not conduct a whole-brain analysis (e.g., ROI based analyses). We also excluded studies with small ($n<10$) sample size, studies with heterogeneous thresholds (e.g., using liberal thresholds in some regions and conservative thresholds in others), and studies from which whole-brain peak information or brain statistical maps could not be retrieved (see **Figure 1** for a flow chart of the literature search).

Data extraction

We obtained original brain statistical maps of the contrast of interest from eight independent datasets included in seven studies (Cano et al., unpublished; Burklund et al., 2017; Lueken et al., 2013; Morgiève et al., 2014; Norman et al., 2020; Price et al., 2018; Reinecke et al., 2014). For the remaining datasets, peak regional coordinates and t-statistics were extracted from the original manuscripts. Literature search, decisions on inclusion, and data extraction were all performed independently by two of the authors and reviewed by the corresponding author. Brain statistical

maps were also inspected to detect artifacts (e.g., during the retrieval of data) and ascertain that matched the results reported in the manuscripts. For each study, several demographic and task-related variables were extracted (**Table 1**).

The sign of the t-statistic or correlation coefficient of a "favorable" response varied between studies depending on whether the response was defined as the change in the score in a severity scale (in which case a negative number would be "favorable") or as the decrease in that score (in which case a positive number would be "favorable"). For this meta-analysis, we implemented "favorable" responses as having a positive sign, and therefore modified the sign of the statistics as necessary.

Meta-analytic approach

The Seed-based d Mapping with Permutation of Subject Images (SDM-PSI) software, version 6.21 (www.sdmproject.com; Albajes-Eizagirre et al., 2019b, 2019a) was used to generate voxel-wise (random effects) effect size maps corresponding to the analyses and contrasts of interest (see **Supplementary Material**). SDM-PSI is a neuroimaging meta-analytic approach that is capable of combining tabulated brain statistical results (i.e., cluster peak statistic and coordinate information) with actual voxel-wise brain statistical maps (Radua *et al.* 2012, 2014).

The main meta-analysis included all studies. When results from more than one contrast were available for a given study, we chose the contrast that was most directly aligned to the outcome measure of interest (e.g., panic symptoms in a panic disorder study) and/or primary functional domain of interest. For instance, we selected the negative vs. neutral condition contrast in emotional processing tasks; high vs. low interference condition contrast in interference tasks; and reappraise vs. look negative condition contrast in emotion regulation

paradigms. The main meta-analysis was repeated after excluding the study by Price et al. (2018) (see below). We also conducted 3 additional (exploratory) meta-analyses for those disorders for which at least 3 datasets were available (i.e., OCD, SAD, and PTSD).

The I^2 index was used to explore the heterogeneity of effect sizes, and publication bias was assessed using a meta-regression by the standard error, analog to the Egger test. For the exploratory meta-analyses, publication bias could not be calculated because of the limited number of datasets (at least 10 datasets are recommended; Sterne et al., 2011). Statistical significance for the main meta-analysis was set at a voxel-level of $p<0.05$ corrected for family-wise error (FWE), and for the exploratory meta-analyses at an uncorrected voxel-level of $p<0.005$. For all analyses a minimum cluster extent of ten contiguous voxels was required. Results are reported in Montreal Neurological Institute (MNI) space.

Results

Included studies and sample characteristics

The main meta-analysis included 17 datasets (6 SAD, 2 PDA, 4 OCD, 4 PTSD, and 1 with general anxiety symptoms) and a total of 442 patients (61.54% females, mean age of 32.42 years, s.d.=9.85). Two datasets from Burklund et al. (2017) study were included, following the original report that compared acceptance and commitment therapy (ACT) to CBT in SAD. We included both datasets in the meta-analysis because ACT is often considered a CBT-based approach (Hayes & Hofmann 2017) and because there were no differences in treatment efficacy between ACT and CBT in the original study (Craske *et al.* 2014). We also included the study by Price et al. (2018) where 91% of participants had one or more diagnosed anxiety-related disorder, although the inclusion criteria did not require a specific diagnosis. This study used

Attention Bias Modification (ABM), which can be part of CBT protocols but could operate through different mechanisms than those typical of CBT (Bar-Haim 2010).

The characteristics of the selected studies, including the contrasts used for each task, are reported in **Table 1.** In 13 datasets emotional processing/regulation tasks were used, two used fear extinction tasks, and the remaining two used executive function tasks. Thus, most of the tasks examined affective neural processes. Two studies (Morgiève *et al.* 2014; Norman *et al.* 2021) compared activation/deactivation effects between CBT-responders and non-responders, while the remaining 15 studies correlated brain activation/deactivation with the degree of response to CBT.

Main meta-analysis

Figure 2 presents the meta-analytic mean map of brain regions showing a positive correlation between BOLD response and clinical response, i.e., activations associated to symptom reduction or deactivations associated to treatment resistance. These regions were the bilateral dorsomedial prefrontal cortex (dmPFC), extending to the dorsal anterior cingulate cortex (dACC) (MNI coordinates = 6, 38, 22, cluster extent = 382, SDM-Z = 5.581), and the right inferior frontal gyrus (IFG) extending to the right anterior insular cortex (AIC) (MNI coordinates = 32, 32, -12, cluster extent = 78, SDM-Z = 5.514). Both results showed no evidence of heterogeneity or publication bias (dmPFC/dACC: $I^2 = 0.56$, Bias test p = 0.217; right IFG/AIC: $I^2 = 0.83$, Bias test p = 0.269). There were no regions showing a significant negative correlation between brain activation and clinical response.

Excluding the ABM study from Price et al. (2018), results remained almost unchanged (right dmPFC/dACC: MNI coordinates = 6, 38, 22, cluster extent = 28, SDM-Z = 4.824; left dmPFC/dACC: MNI coordinates = -8, 46, 4, cluster extent = 16, SDM-Z = 4.747; right IFG: MNI coordinates = 32, 32, -12, cluster extent = 16, SDM-Z = 4.867), although a new significant cluster emerged in the left inferior parietal lobule (IPL) (MNI coordinates = -54, -52, 38, cluster extent = 15, SDM-Z = 4.942) (**Supplementary Figure 1**). These results did not show evidence of heterogeneity or publication bias (right dmPFC/dACC: $I^2 = 0.7$, Bias test p = 0.136; left dmPFC/dACC: $I^2 = 0.74$, Bias test p = 0.251; right IFG: $I^2 = 2.07$, Bias test p = 0.227; left IPL: $I^2 = 5.4$, Bias test p = 0.067). Excluding the Burklund et al. (2017) ACT study, the main results were maintained, but significant clusters were larger (bilateral dmPFC/dACC: MNI coordinates = 2, 38, 20, cluster extent = 553, SDM-Z = 5.51; right IFG: MNI coordinates = 32, 28, -8, cluster extent = 196, SDM-Z = 5.911), and a new significant cluster emerged in the left IFG (MNI coordinates = -50, 32, 14, cluster extent = 33, SDM-Z = 4.911) (**Supplementary Figure 2**). These results did not show evidence of heterogeneity or publication bias (bilateral dmPFC/dACC: $I^2 = 0.71$, Bias test p = 0.544; right IFG: $I^2 = 4.27$, Bias test p = 0.152; left IFG: $I^2 = 4.67$, Bias test p = 0.259).

To facilitate comparison with the disorder-specific meta-analyses described below, **Supplementary Table 1** and **Supplementary Figure 3** show the results of the main meta-analysis at an uncorrected threshold.

Disorder-specific (exploratory) meta-analyses

As mentioned earlier, we conducted separate meta-analyses for OCD (n=4, 77 patients), SAD (n=6, 161 patients), and PTSD (n=4, 100 patients).

Supplementary Table 2 and **Supplementary Figure 4** summarize the regions showing a positive correlation between BOLD response and CBT outcome in OCD. These included the IFG, anterior and posterior insula, caudate and thalamus bilaterally, the dmPFC, the left inferior and middle temporal gyri (ITG and MTG, respectively), the left cuneus, the right supramarginal gyrus, the left putamen, the right middle frontal gyrus (MFG), and the right supplementary motor area (SMA).

Regarding SAD, a number of regions showed a positive correlation between BOLD response and CBT outcome: the bilateral rolandic operculum, the subgenual ACC, the right precentral gyrus, the right dorsolateral prefrontal cortex (dlPFC), the right SMA, and the posterior cingulate cortex (PCC) (**Supplementary Table 3** and **Supplementary Figure 5**).

Finally, there were no significant results for the PTSD meta-analysis.

Discussion

To our knowledge, this is the first preregistered meta-analytical investigation of the neural predictors of CBT outcome in anxiety-related disorders based on whole-brain results of task-based fMRI studies. Across different emotional processing paradigms, we observed that the BOLD response in a network of regions involved in salience and interoception processing, encompassing frontal and limbic cortices (i.e., the right IFG-AIC, the dmPFC-dACC), was robustly associated with a positive CBT outcome. Importantly, in the original studies included in this meta-analysis, mainly activation and only occasionally deactivation was reported in the analysis of the average brain response to the task. Thus, we may assume that most of our meta-analytical results refer to activation associated with symptom reduction (rather than deactivation associated with no symptom reduction).

The brain regions identified in our main meta-analysis have been highlighted as critically involved in diverse aspects of (pathological) anxiety. Thus, the IFG, together with the adjacent AIC, conveys representations of bodily arousal states, whose misinterpretation may lead to increased anxiety appraisals (Paulus & Stein 2006). Likewise, neural activity in regions of the medial wall, including the dmPFC and the dACC, has been related to numerous processes allegedly relevant for pathological anxiety, such as intolerance of uncertainty (Volz *et al.* 2003; Schienle *et al.* 2010); conscious threat appraisal (Grupe & Nitschke 2013; Kalisch & Gerlicher 2014); cognitive monitoring and control processes, including error monitoring (i.e., negative reward prediction errors) (Hauser *et al.* 2017); and overall emotion regulation (Uchida *et al.* 2014). In this regard, self-reported reappraisal has been shown to correlate positively with activity in the dmPFC, whose activation during emotional processing correlates negatively with amygdala activation (Drabant *et al.* 2010). Also, a recent meta-analysis of our group described that medial wall regions, in combination with the AIC, participate in a domain-general regulatory network important for both effortful (i.e., cognitive reappraisal) and automatic (i.e., fear extinction) regulation strategies (Picó-Pérez *et al.* 2019). On the other hand, the dorsal ACC (Ge *et al.* 2017), as well as the ACC more generally (Vai *et al.* 2016; Tian *et al.* 2020; Tsolaki *et al.* 2021), have been implicated in predicting treatment response across different therapies in affective disorders (Pizzagalli 2011). This points to a potential general role of the ACC in predicting treatment response regardless of the treatment and, to a certain extent, of the disorder, perhaps by mediating the recovery of those regions specifically altered in each disorder.

The different functions subserved by these regions have been elegantly combined into a single process using a computational neuroscience perspective (Korn & Bach 2019). In this study, the authors showed that the deployment of an optimal policy to deal with approach-

avoidance conflicts -involving numerous and complex computations aimed at minimizing threats and maximizing rewards- is positively associated with neural activity in a network of regions that includes all the brain clusters arising from our main analysis: the dmPFC, the dACC and the IFG. Although in Korn and Bach (2019) study other brain regions (e.g., bilateral posterior thalamus and medial occipital cortex) were also activated, they were probably related to the visual attention demands of the task. Likewise, Korn and Bach (2019) also described bilateral IFG activations, while we only observed significant positive correlations in the right hemisphere (although the left IFG also appeared when excluding the dataset using ACT). Nevertheless, in that study, activations in the right IFG were more prominent and extended than in the left IFG, suggesting that, as we have observed here, IFG may be partially lateralized to the right hemisphere when the tasks involve mainly non-verbal stimuli. Moreover, recent reports have suggested that disruptive effects of anxiety on attentional networks are lateralized to the right IFG (Cheng *et al.* 2021).

The results from our meta-analysis thus suggest that in populations with anxiety-related disorders, preserved levels of brain activity during emotional processing in the medial wall and the right IFG facilitate CBT response. Neural activity in these regions may regulate limbic responses in front of emotional stimuli, and, indeed, deficits in inhibitory coupling between medial wall regions and the amygdala predict a worse CBT outcome (Lueken *et al.* 2013). As reviewed above, the behavioral consequences of the activation of these cortical areas include, among others, displaying higher levels of tolerance to uncertainty, showing an appropriate threat estimation, or non-disrupted emotion regulation capacities, which will certainly result in a facilitative interaction with CBT. Nevertheless, it seems that the computational concept of optimal approach-withdrawal policy may more critically account for CBT success.

When we analyzed the different disorders separately, we found novel significant findings for two of them (OCD and SAD). For OCD, the significant brain regions went beyond the transdiagnostic core regulatory regions of the main analysis. Some of the regions found to be predictive of CBT outcome have also been shown to participate in emotion regulation processes, which may be triggered by the negatively valenced stimuli used in most of the OCD protocols (i.e., symptom provocation). This may be the case of the supramarginal gyrus (Buhle *et al.* 2014; Ochsner & Gross 2014), the SMA (Picó-Pérez *et al.* 2019), as well as the ITG, the MTG and the MFG (see Picó-Pérez et al., 2017). Correlation between BOLD response and clinical response in other regions, such as the thalamus, may be related to attentional processes and visual stimuli processing, whereas insula and striatal activations (i.e., caudate and putamen) are typically observed in symptom provocation and emotion induction protocols in OCD (Picó-Pérez *et al.* 2020; Soriano-Mas 2021).

Regarding the BOLD response/clinical response correlation observed in SAD studies, some of them, such as SMA or dlPFC findings, may be also related to the deployment of different emotion regulation strategies (Etkin *et al.* 2015). Specifically, dlPFC activation has been shown to play a key role in supporting the manipulation of appraisals in working memory (Buhle *et al.* 2014), whereas the precentral gyrus and the rolandic operculum could participate in cognitive control networks (Wong *et al.* 2019). Interestingly, in SAD patients we also observed significant correlations in regions that may be included within the so-called default mode network (i.e., the subgenual ACC and the PCC), whose activity critically accounts for self-referential and self-evaluative mental processes (Buckner *et al.* 2008). Notably, patients with SAD have been described to present abnormalities in DMN activity (Northoff 2020), and it is therefore not surprising that preserved activations in these regions during task protocols

involving self-evaluative components, such as the ones used in most of the studies with SAD patients reviewed here, are associated with better CBT outcome.

These disorder-specific findings are likely related to potential pathophysiological mechanisms of the disorders, as well as to the nature of the tasks used in the assessment of these populations, which may certainly account, at least partially, for the different regions associated to CBT outcome in these two disorders. In any case, it is worth noting that we have always observed positive associations between regional activations and CBT outcome, which, overall, may reflect that patients with better task engagement, including perceptive and attentional levels and allegedly leading to increased emotional reactivity, will benefit more from CBT. Some classical theoretical accounts have already indicated that enhanced emotional activation would be a prerequisite for effective CBT in anxiety-related disorders (Foa & Kozak 1986). Our results suggest that activation in regions supporting the deployment of different kind of emotion regulation strategies is also a predictor of CBT outcome.

Certain regions did not emerge as significant predictors of CBT outcome, despite being regularly emphasized in functional imaging studies of anxiety-related disorders (e.g., amygdala). Typically, studies implicating amygdala involvement in these disorders have utilized region-of-interest (ROI) approaches to identify significant effects. Our meta-analysis followed current recommendations which favor the exclusion of ROI-focused studies in order to prevent bias in study selection. The exclusion of these studies would not be expected to prevent detection of reliable effects in small structures, particularly subcortical structures, as the integration of whole-brain data in previous meta-analyses has proven effective in mapping such effects, including providing novel observations (Fullana *et al.* 2016). More broadly, we recognize that the brain

regions linked to treatment outcome may be distinct from those that characterize general differences in brain function between patient and controls (see Fullana & Simpson, 2016).

Our study has several strengths: we focused only on whole-brain studies; obtained original brain maps for almost half of the studies included; and conducted additional analyses to check the robustness of our results. The main limitation is that we could not conduct separate analyses for each task domain (and for some individual disorders), due to insufficient study number. The inclusion of more symptom provocation studies will be an important extension to the current work, as these paradigms arguably provide more ecologically validity in anxiety-related disorders. Moreover, as in any other meta-analysis, selection bias might have played a role in our study and limited the generalizability of our results. Finally, the brain activations found here might not be explicitly predicting the effect of CBT alone since other non-treatment related ("unspecific") effects may influence CBT outcome.

Despite these limitations, our study contributes to the characterization of neul predictors of CBT outcome in anxiety-related disorders. Likewise, meta-analytic studies provide a strong basis to expand the work in different future directions. For instance, present results may be compared with other studies/meta-analysis of neural treatment outcome predictors in other treatment modalities (e.g., pharmacological) or in other disorders. They may also help in the identification of system targets for novel interventions that may be combined with CBT to develop optimized protocols, which may be then properly validated in controlled clinical trials. This should eventually lead to the development of imaging biomarkers of treatment response and to better personalized approaches for the treatment of mental disorders.

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Conflicts of interest

None.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Figure Captions

Figure 1. PRISMA flow diagram of studies included in the meta-analysis. Note: PRISMA = Preferred reporting items for systematic reviews and meta-analyses (http://www.prismastatement.org/).

Figure 2. Regions showing positive correlation between baseline BOLD response and clinical response across anxiety-related disorders. Results from the main meta-analysis ($p<0.05$ FWE corrected).

Table 1. Characteristics of the 17 fMRI datasets included in the meta-analysis.

	Disorder	N	Mean age (SD)	Females (N)	Medicated (N)	Outcome measure	Score pre-CBT[1] (SD)	Score post-CBT (SD)	Length of treatment (sessions/ duration)	fMRI task	Contrast included
Aupperle et al., 2013	PTSD	14	40.07 (7.44)	14	0	CAPS	66.07 (16.78)	16.29 (16.81)	11/90´	Affective stimuli anticipation	Affective processing > Baseline
Bryant et al., 2020	PTSD	37	41.11 (11.1)	17	10	CAPS	67.8 (19.1)	28.4 (20)	9/60-90’	Cognitive reappraisal	Reappraisal > Watch
Burklund et al., 2017 sample 1*	SAD	16	26.54 (10.28)	7	2	LSAS-SR	80.5 (18.55)	55.93 (23.86)	12/60´	Rejection	Rejection > Neutral
Burklund et al., 2017 sample 2*	SAD	19	27.48 (5.23)	9	3	LSAS-SR	87 (20.07)	61.61 (24.07)	13/60´	Rejection	Rejection > Neutral
Cano et al., unpublished*	OCD	14	39.36 (12.85)	8	12	YBOCS	26.14 (5.17)	16.43 (6.71)	20/90-120’	Fear conditioning and extinction	Early CS+ > Early CS- (conditioning)
Doehrmann et al., 2013	SAD	39	29.3 (7.9)	14	0	LSAS	81.8 (13.4)	40.8 (18.1)	12/60´	Emotional processing (faces)	Angry > Neutral
Falconer et al., 2013	PTSD	13	38.3 (12.16)	8	6	CAPS	75.5 (NA)	38.6 (NA)	8/90´	Go/No Go (inhibition)	No Go > Go
Fonzo et al., 2017	PTSD	36	34.42 (10.23)	23	3	CAPS	66.33 (15.17)	29.6 (21.26)	9-12/90’	Emotional reactivity	Conscious fear > Neutral
Klumpp et al., 2014	SAD	21	24.9 (6.3)	15	2	LSAS	72.5 (11.6)	50.4 (19.5)	12/60´	Emotional face matching	Faces > Shapes
Klumpp et al., 2016	SAD	32	25.4 (5.1)	24	0	LSAS	74.3 (14.9)	47.9 (20.4)	12/60´	Cognitive control	Angry > Neutral
Klumpp et al., 2017	SAD	34	25 (4.7)	22	0	LSAS	77.7 (14)	47.3 (23.3)	12/60’	Cognitive reappraisal	Reappraisal > Look Negative
Lueken et al., 2013*	PD	49	35.27 (10.43)	33	0	HARS	24.59 (5.28)	13.10 (6.96)	12/NA	Fear conditioning and extinction	CS+ > CS- (extinction)
Morgiève et al., 2014*	OCD	31	36.6 (NA)	18	17	YBOCS	25.4 (4.7)	14.1 (7.7)	15/45´	Symptom provocation	Provocation > Neutral
Norman et al., 2020*	OCD	20	32.34 (NA)	12	10	YBOCS	23.88 (NA)	11.73 (NA)	12/NA	Incentive flanker	High > Low interference
Olatunji et al., 2014	OCD	12	32.25 (9.92)	6	9	YBOCS	32.25 (5.73)	23.58 (6.63)	24/NA	Symptom provocation	Early provocation > Neutral

Price et al., 2018*	Anxiety[2]	41	30.85 (9.54)	32	0	CAPS Hypervigilance	4.54 (2.03)	3.9 (1.97)	8/15’	Emotional reactivity	Negative > Neutral
Reinecke et al., 2014*	PD	14	37.2 (11.1)	10	0	PDSS-SR	10.5 (6.3)	4.2 (4)	4/NA	Emotion regulation	Negative > Neutral

Abbreviations: fMRI: functional magnetic resonance imaging; SD: standard deviation; CBT: cognitive-behavior therapy; PTSD: post-traumatic stress disorder; CAPS: Clinician-administered PTSD scale; SAD: Social anxiety disorder; LSAS-SR Liebowitz Social Anxiety Scale-self report; HARS; Hamilton rating scale for anxiety; PD: panic disorder; OCD: obsessive-compulsive disorder; YBOCS: Yale-Brown obsessive-compulsive scale; NA, not available.

[1]CBT was individually delivered in all studies except in Falconer et al. (2013) and Cano et al. (unpublished), where it was delivered in group.

[2]Participants were included in this study based on their scores on the Spielberger State-Trait Anxiety Inventory-Trait Form (STAI-T) but 91% fulfilled diagnostic criteria for an anxiety-related disorder.

*Original statistical brain maps available.